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09/341,407	10/12/99	DELOVITCH	T 087300-00040

EXAMINER	
ROARK, J	
ART UNIT	**PAPER NUMBER**
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DATE MAILED: 02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/341,407	DELOVITCH, TERRY L.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover she t with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *7 and 10-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed on Oct. 12, 1999 (Paper No. 5), is acknowledged.
Claims 19, 20, 23, 27, 28 and 31 have been amended.
Claims 1-31 *are pending.*

2. Applicant's election with traverse of Group I, claims 1-6 and 8-9 with a species election of diabetes in Paper No. 9 is acknowledged.

The traversal is on the following grounds. First, it is argued that it is improper to impose a restriction requirement on a single claim. Applicant points to In Re Weber, Soder and Boksay (198 USPQ 328, 331 (CCPA 1978)) in particular for support of this argument. Second, Applicant also asserts that there is no undue burden in regrouping the method and composition claims on the grounds that a search for one would encompass the other.

Neither argument is found persuasive. As stated in Section 2 of Paper No. 7, the anti-CD28 antibody and B7.2 protein encompassed by the term "agonist" differ in structure and mode of action. Even in the case of Markush groups (the topic of MPEP 803.02 in which In re Weber is discussed), it is recognized that lack of unity exists between compounds of a Markush-type group *when the compounds do not share a substantial structural feature* (See MPEP 803.02). No shared structural feature exists between an anti-CD28 antibody and a B7.2 protein. Given the lack of a shared substantial structural feature among the compounds comprising the active ingredient of each of the instant pharmaceutical compositions; insufficient grounds for an examination as alternate species exists.

With respect to the argument that no undue search burden exists; the Examiner acknowledges that the methods and particular pharmaceutical compositions are classified in the same class and subclass. However, as set forth in Sections 5-7 of Paper No. 7, the instant pharmaceutical compositions can be used in the multiple methods recited in the claims, as well as in various unrecited methods. Consequently, a search for each pharmaceutical composition is not co-extensive with a search for a particular method of use. Therefore, a prima facie showing of burden of search was established in Paper No. 7.

The requirement is still deemed proper and is therefore made FINAL.

Given the previous restriction requirement, which is hereby reiterated; claims 7 and 10-31 have been withdrawn from consideration by the examiner under 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1-6 and 8-9, as they read on an anti-CD28 antibody with a species election of diabetes, *are under consideration in the instant application.*

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). *Applicant should amend the first line of the specification to indicate priority is claimed under 35 U.S.C. 371 to PCT/CA98/00015.*

4. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

7. The drawings filed on 10/12/99 are acceptable.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing development of autoimmune diabetes in the NOD mouse, does not reasonably provide enablement for a method of preventing development of other autoimmune diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach how to effectively prevent the development of autoimmune diseases other than diabetes, especially in humans, by administering an anti-CD28 antibody or other CD28 agonists. The specification does not teach how to extrapolate data obtained from studies of preventing autoimmune diabetes in the NOD mouse model to the prevention of other autoimmune diseases, commensurate in scope with the claimed invention. One skilled in the art would not recognize that a method of preventing diabetes in the NOD model system could be generalized for the prevention of the various autoimmune diseases recited, because the different autoimmune diseases involve distinct antigens and different types of autoimmune responses. For example, it was well known in the art at the time the invention was made that diabetes is an organ specific disease mediated by T cells, whereas SLE is a systemic disease mediated by antibodies and immune complexes. Differences were recognized by the skilled artisan at the time of the invention even between two T cell-dependent autoimmune diseases: in diabetes treatment with an antibody to the CD28 ligand B7.2 prevented disease, whereas in EAE (an animal model of multiple sclerosis) antibody to B7.2 increased disease severity (reviewed in Thompson Cell 81:979-982 1995, IDS #AO, see entire document, especially page 980, 2nd column).

In the absence of working examples or other reasonably predictive evidence, the skilled artisan could not reasonably predict the efficacy of the method exemplified in the specification in preventing autoimmune diseases other than diabetes. Therefore, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

11. Claims 1-6 and 8-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing development of autoimmune diabetes in the NOD mouse model, does not reasonably provide enablement for a method of preventing development of autoimmune diabetes in humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not adequately teach how to effectively prevent the development of autoimmune diabetes in humans by administering an anti-CD28 antibody or other CD28 agonists. The specification does not teach how to extrapolate data obtained from studies of preventing autoimmune diabetes in the NOD mouse model, commensurate in scope with the claimed invention. One skilled in the art would not have recognized that a method of preventing diabetes in the NOD model system could be applied as a method of preventing autoimmune diabetes in humans because genus-specific differences were well known to the skilled artisan at the time the invention was made.

For example, Bowman et al. (Immunology Today 15:115-120 1994) indicate that the genetic homogeneity of the NOD mouse makes interventional studies straight-forward; whereas the genetic heterogeneity of humans populations, the broad range of ages for disease onset, and the difficulties associated with detecting individuals during the pre-symptomatic window makes interventional studies in humans uncertain (see entire document, especially 2nd column page 115). In addition, given the heterogeneity of the disease response in humans, there is a high level of uncertainty as to whether intervention at the recited age of from about 6 months to 2 or 3 years of age would be effective for any given individual. As disclosed in the specification on page 27 at lines 16-19, the stage of disease development at which anti-CD28 therapy is administered is critical: delaying administration of anti-CD28 from the 2-4 week period to the 5 week timepoint provided significantly less protection from development of diabetes in the NOD mouse model. Consequently, in order to have a reasonable expectation of success in preventing the development of diabetes in humans, the skilled artisan would have to be able to clearly identify both that an individual was at risk and that disease had not already progressed beyond a window corresponding to the 2-4 week period in the NOD mouse.

Thus, the disclosure does not appear to provide adequate enabling support for preventing the development of diabetes in humans. The skilled artisan could not reasonably predict the efficacy of the method exemplified in the specification in preventing autoimmune diabetes in subjects other than the NOD mouse, especially in such a heterogeneous population as humans. Therefore, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

12. For the purpose of examination under 35 U.S.C. 103, the claims are examined only with respect to the enabling disclosure of a method for preventing the development of diabetes in the NOD mouse model by administering anti-CD28 antibody; thus the rejection does not apply to claim 5 and dependent claims 6, 8 and 9 which limit the method to human subjects.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over
Rabinovitch (Diabetes 43:613-621 1994, IDS-AH)
in view of Lenschow et al. (Immunity 5:285-293 Sept. 1996, IDS-Y),
and in further view of *either*
King et al. (Eur. J. Immunol. 25:587-595 1995, IDS-W), *or*
Webb et al. (Blood 86:3479-3486 1995, IDS-AQ).

The claims are drawn to a method of preventing diabetes in the NOD mouse by administering a monoclonal antibody that is a CD28 agonist.

Rabinovitch teaches that multiple immunostimulatory procedures prevent IDDM (autoimmune diabetes) in the NOD mouse (see entire document, e.g., "Title"). Rabinovitch also teaches that the immunostimulation protects from diabetes by favoring T cell differentiation along a protective TH2 pathway, thus downregulating the destructive TH1 response (e.g. page 616-619 "Immunostimulatory Procedures Prevent IDDM: Correction of a Cytokine Balance?", especially page 618-619 bridging paragraph). Rabinovitch concludes that the findings in the NOD mouse provide a basis for considering immunostimulation in attempts to prevent IDDM (autoimmune diabetes) in humans at risk for this disease (e.g., concluding paragraph page 619).

Rabinovitch does not teach an agonistic anti-CD28 antibody.

Lenschow et al. also teach that the absence of signaling through CD28 in the NOD mouse leads to an accelerated development of diabetes due to the development of a dominant TH1 response (e.g., "Discussion" page 290, especially end of 1st full paragraph).

Lenschow et al. further teach that the increased incidence of diabetes occurs when signaling through CD28 is blocked during the first two weeks of life (e.g., page 290, 2nd column, bottom ¼ of text).

Both King et al. and Webb et al. teach that a CD28 agonist monoclonal antibody induces a TH2 response (see entire document of each, especially "Abstract" and "Methods").

Given the teachings of the references, the ordinary artisan at the time the invention was made would have been motivated to treat NOD mice with an agonistic anti-CD28 antibody with the expectation of stimulating the development of a TH2 response and thus preventing the development of diabetes. The teachings of both King et al. and Webb et al. show that the ordinary artisan at the time the invention was made would have recognized that an antibody could be used to stimulate CD28, and further that this stimulation results in the TH2 type of response that both Rabinovitch and Lenschow et al. teach protects from diabetes. Consequently, the teachings of the references also indiacte that the ordinary artisan would have had a reasonable expectation of success in preventing development of diabetes in the NOD mouse. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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February 8, 2001

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